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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,410	12/14/2001	Peggy J. Farnham	960296.97401	1459

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,410	FARNHAM ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *1 and 5-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4, 11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's reply filed on 03/18/2005 is acknowledged.

Claims 1-13 are pending. Claims 1, and 5-10 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The newly amended claims 11-13 are partially drawn to group 1, i.e. protein group. Note the restriction requirement mailed on 08/11/2004.

Claims 2-4, and 11-13 are examined under consideration. As stated before in the previous Office action, claims 11-13 are examined to the extent they are drawn to the elected invention.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office action contains new grounds of rejection,

Claim Objections, Maintained

Claims 11-13 are objected to because of the following informalities: the claims are drawn to multiple inventions. Applicant argues that the claims have been amended to obviate the objection of record. Applicant is reminded that the elected invention is drawn to nucleic acids, not proteins. Claim 11 previously drafted appear to have two main ingredients, i.e. antibody binding to the protein by the claimed invention and the claimed nucleic acids. The restriction was set forth accordingly. Note the Office actions mailed on 08/11/2004, and 12/01/2004. Claim 11 as currently construed is drawn to two main ingredients, i.e. polypeptide and nucleic acids.

Claim Rejections - 35 USC § 101, Withdrawn

The rejection of claim 2 under 35 USC 101 is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112

Claims **12, and 13 remain rejected** under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Rejection of claim 2 is withdrawn in view of the amendment.

Claims 12, and 13 recite "a quantitatively predetermined level of expression" but it is not clear what the metes and bounds are. One in the art would have difficulty to determine whether adding liver tumor cells from liver cancer patients in a kit would infringe on the claimed invention.

The specification at paragraph [0019] discloses:

> In still another aspect, the invention can relate to a kit having use in a method for determining in a tumor or other cell the expression level of the polypeptide or of a nucleic acid encoding the polypeptide. The kit can contain one or more antibody directed to an epitope on the polypeptide and one or more oligonucleotide or polynucleotide that hybridizes to the nucleic acid that encodes the polypeptide. The kit can also further include additional components for use as positive or negative controls in a method for determining the expression level. Such additional components can include samples of tumor or non-tumor liver cells, or an extract of any of the foregoing, for which a level of expression of a polypeptide or a polynucleotide of the invention has been determined. Alternatively or additionally, the kit can contain a sample of one or more of a polypeptide, a polynucleotide, and an oligonucleotide of the invention for quantification purposes.

This disclosure does not give any guidance on what "a quantitatively predetermined level of expression" would be, for example, in the scale of 1-10.

For the compact prosecution purpose, the Office will assume that the unclear limitation means any liver cancer cells having a higher gene expression for claim 12, and any normal liver cells having a lower gene expression as compared to that of the

liver cancer cells for claim 13. However, this treatment does not relieve applicant the burden of responding to this rejection.

Claims 2-4, and 11-13 **remain rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description** requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2-4, and 11-13 are interpreted as drawn to a genus of nucleic acid molecules with various degrees of variations, i.e. 80 % identity to the coding sequence of SEQ ID NO: 1, and 3, and hybridizing molecules under the recited conditions to the coding sequence of SEQ ID NO: 1, and 3, or 80 % identity to the coding sequence of SEQ ID NO: 1, and 3.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004).

Applicant argues that the specification provides identifying characteristic of the claimed genus at paragraph [0009], where it teaches that the mouse sequence (SEQ ID NO:1), and the human mouse sequence (SEQ ID NO:3) are at least 85 % identical (in fact 87% identical), and the proteins translated from those two cDNAs (i.e. SEQ ID

NO:1, and 3) are 91% identical, and several stretches of the mouse protein encoded by SEQ ID NO:1 contain putative transmembrane domains, and SEQ ID NO:1 is related to sequences found in C. elegans and D. melanogaster, which suggest a conserved function for the polynucleotide.

These arguments have been fully considered but found unpersuasive. First, applicant's argument with SEQ ID NO: 1, and 3 is not commensurate in scope of the claims because the claims as currently construed are not limited to the two species that the specification provides the required written description for. It is noted that the argument with sequences of C. elegans and D. melanogaster is not commensurate in the scope of the claims, either because those sequences appear to outside the scope of the claimed invention in light of the teachings of the specification. The specification as originally filed does not disclose the claimed invention is drawn to nucleic acids of sequences of C. elegans and D. melanogaster.

During the prosecution history, the Office has not disputed the fact that the specification provides an adequate written description for the two species (SEQ ID NO: 1, and 2). However, all other species that belong to the genus (i.e. 80 % identity to the coding sequence of SEQ ID NO: 1, and 3, and hybridizing molecules under the recited conditions to the coding sequence of SEQ ID NO: 1, and 3, or 80 % identity to the coding sequence of SEQ ID NO: 1, and 3) are partial structures without any identifiable associated function. The specification must provide sufficient distinguishing identifying characteristics of the genus other than the partial structures in order to provide an adequate written description. The specification fails to provide functional

characteristics, and/or structure/function correlation for the claimed genus. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of nucleic acid molecules, given that the specification has only described SEQ ID NO: 1 and 3. Therefore, only isolated nucleic acid comprising SEQ ID NO: 1 and 3, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims **2-4, and 11-13 remain rejected** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 1, 3, and nucleic acids encoding SEQ ID NO: 2, and 4, does not reasonably provide enablement for any other nucleic acid molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is □undue□ include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The scope of enablement rejection is made because the nature of the invention is interpreted as drawn a genus of nucleic acid molecules with certain degree of similarity to SEQ ID NO: 1 or 3.

Applicant argues that based on the state of the art at the time of filing, using the specification, one of ordinary skill in the art would have been able to identify similar polynucleotide sequences show differential expression in liver tumor cells as compared to normal liver tissue cells, and used them as markers for identifying tumors. The specification discloses that gene expression in a liver tumor and in regenerating liver tissue could be determined by various art-known methods as disclosed at paragraphs [00028]-[00030]. The specification at paragraph [00032]-[00044] discloses how to make and use the claimed polynucleotide and polypeptide sequences. The specification provides a skilled artisan with the ability to assess expression levels of the claimed polynucloeotids and proteins.

These arguments have been fully considered but found unpersuasive. First, applicant argument that the specification at paragraph [00032]-[00044] discloses how to make and use the claimed polynucleotide and polypeptide sequences is not commensurate in scope of the claims. The Office already indicated in the previous Office action that SEQ ID NO: 1 and 3 are enabled. However, the rest of the claimed similar polynucleotide sequences yet to be identified by the art-known screening method using the disclosed SEQ ID NO: 1, and 3 (i.e. polynucleotide showing differential expression in liver tumor cells as compared to normal liver tissue cells that can be used as markers for identifying tumors) is not enabled. It is noted that law requires that the

disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

As stated in the previous Office action, the specification at pages 8 and 9 teaches that SEQ ID NO: 1 is over-expressed in mouse HCC (hepatocellular carcinoma) and SEQ ID NO: 3 is also over-expressed in human HCC. However, the specification does not teach which other nucleic acid molecules other than SEQ ID NO: 1 and 3 are expressed in HCC. The specification does not teach how to use the claimed nucleic acids that are not over-expressed in HCC. The specification does not teach how to use and make other species

The relative level of skill in making nucleic acid molecules that are over-expressed in HCC is low. Graveel et al., (IDS, 2001, Oncogene, vol. 20, pages 2704-2712) teach the current state of how one of skill isolates a nucleic acid that is over-expressed in HCC. It requires screening a large quantity of clinical samples, namely liver tissue from patients with HCC, followed by isolating mRNA species that are differentially and preferentially expressed in HCC. In other words, one skilled in art has to determine what other mRNA species are differentially or preferentially expressed in HCC. Which other similar sequences could be used as HCC or cancer marker is still unpredictable until said sequences are experimentally determined by screening a large quantity of appropriate clinical samples.

The breadth of the claimed invention is broad including many unknown species.

The level of predictability, which nucleic acid molecule resembling the coding sequence of the instant SEQ ID NO: 1 will be expressed in HCC or is low as shown by

Graveel et al (2001). It requires experimental determination if they ever exist. The amount of direction or guidance by the inventor how to use the full scope of claimed nucleic acid molecule with the recited partial structural element is limited. There is not adequate guidance or direction to allow the person of ordinary skill in the art to make the claimed nucleic acids in a manner commensurate in scope with the claims. The quantity of experimentation needed to make the invention is large. In order to make the full scope of the invention, one skilled in the art has to screen a large quantity of clinical samples from liver or pancreatic tissue of patients having HCC, followed by sequence the nucleic acid composition. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

How to use the claimed nucleic acids that are 80 % identical to the coding sequence of SEQ ID NO:1, or 3, and the hybridizing molecules not expressed in HCC requires undue experimentation because the specification does not teach how to use the vast number of claimed nucleic acids other than SEQ ID NO:1 or 3. Limiting the scope to the enabled species, i.e. SEQ ID NO: 1 and 3 would obviate this scope of enablement rejection.

Claim Rejections - 35 USC § 102, Maintained

Claims 2-4, 11, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonaldo et al., (1996, Genome Research, vol. 6, pages 791-806).

The claims are interpreted as drawn to an isolated nucleic acid, vector comprising said nucleic acid, host cell comprising said vector, and a kit comprising said

nucleic acid, wherein said nucleic acid is a nucleic acid hybridizes under the newly amended hybridizing conditions to the nucleic acid sequence of murine CRG-L1 (SEQ ID NO:1) encoding a polypeptide of about 275 amino acids with a predicted molecular weight of about 30 to 35 kDA (i.e. SEQ ID NO: 2), wherein said nucleic acid is downstream from a heterologous promoter (claim 3), transfected into a host cell (claim 4), wherein the kit contains positive control and negative control (claim 11), more specifically, said negative control being non-tumor liver cells (claim 13).

Applicant argues that the Office mischaracterize the claimed invention as well as the prior art of record, and then goes on saying that applicant amended the claims in order to obviate the rejection of record, and further states that the amended claims are not anticipated by Bonaldo et al., (1996).

These arguments have been fully considered but found unpersuasive. The specification at the first sentence of paragraph [0025] discloses "Structurally, the nucleic acid sequence of murine CRG-L1 (SEQ ID NO:1) encodes a polypeptide of about 275 amino acids with a predicted molecular weight of about 30 to 35 kDA." Since the instantly claimed nucleic acid is drawn to a nucleic acid that hybridizes to SEQ ID NO:1 comprises poly A tails (about 20 A's) at the C-terminal end of SEQ ID NO:1, the instantly claimed nucleic acid reads on the poly (dT) primers of Bonaldo et al. It is the Office's position that the poly (dT) primers of Bonaldo et al., would hybridizes to the C-terminal poly A tails of the instant SEQ ID NO: 1 encoding SEQ ID NO:2. As stated in previous Office action, Bonaldo et al., at page 801, right column under the heading "Construction of Directionally Cloned cDNA Libraries" teach "*Not*I-tag-$(dT)_{18}$ and other

poly(dT) primers for priming the first strand of cDNA synthesis. Further, Bonaldo et al., teach at page 802, Figure 6 that pT7T3 vector that the first strand of cDNA is being inserted to, wherein the pT7T3 vector has a heterologous promoter (i.e. T7 or T3 promoter in relationship to human cDNA made from priming the total cellular RNA from the various sources for the subtractive cDNA library construction. Since the subtractive construction requires two sources of controls (i.e. positive and negative for the expressions), the claimed positive and negative controls read on the tissues samples of Bonaldo et al. As for non-tumor live tumor cells and an extract of non-tumor cells, Bonaldo et al., teach extracts from fetal spleen or fetal liver. Note the abstract.

Thus, Bonaldo et al., anticipate claims 2-4, 11, 13.

Claims 2, and 11-13 remain rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al., (April 12, 1996, Biochim Biophys Acta. Vol. 1315, issue no. 3, pages 169-75).

The claims are interpreted as drawn to an isolated nucleic acid, and a kit comprising said nucleic acid that hybridizes under the stringent conditions to SEQ ID NO:1, wherein said kit contains positive control and negative control (claim 11), more specifically said positive control being liver tumor cells (claim 12), said negative control being non-tumor liver cells (claim 13).

Applicant argues that Wu et al., report the identification of 36 up- and down-regulated cDNAs from HCC and normal liver, but does not disclose the instantly claimed

invention, then applicant goes on saying that applicant amended the claims to recite the coding sequence of SEQ ID NO: 1, and 3.

These arguments have been fully considered but found unpersuasive because applicant's argument is not commensurate in scope of the claims. As stated above, the specification at the first sentence of paragraph [0025] discloses "Structurally, the nucleic acid sequence of murine CRG-L1 (SEQ ID NO:1) encodes a polypeptide of about 275 amino acids with a predicted molecular weight of about 30 to 35 kDA." Since the instantly claimed nucleic acid is drawn to a nucleic acid that hybridizes to SEQ ID NO:1 comprising poly A tails (about 20 A's) at the C-terminal end of SEQ ID NO:1, the instantly claimed nucleic acid reads on the poly (dT) primers of Wu et al., which are used to isolate 36 up- and down-regulated cDNAs from HCC and normal liver

As stated before in the previous Office action, Wu et al., at page170 left column teach "oligo(dT) cellulose (Boehringer, Almere, The Netherlands)" that is used to isolate poly(A) containing mRNA, and "Oligo(dT)-Not1 (Invitrogen, San Diego, CA)" that is used to prime the first strand of cDNA synthesis. Further, Wu et al., teach kit containing positive control and negative control, more specifically said positive control being liver tumor cells, said negative control being non-tumor liver cells. Note Fig. 1, and Materials and methods at page 170.

The Following Are New Grounds of Rejection

Claim Rejections - 35 USC § 112

Claims 2-4, 11-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This new matter description rejection is made because of the newly added limitation "80 % identity to the coding sequence of SEQ ID NO: 1, or 3" in the base claims 2, and 11. Applicant is kindly request to point out the support for the newly added limitation since the support is not apparent to the Office. It is noted that the Office is able to find support for "at least about 85% nucleotide sequence identity to the coding sequence of SEQ ID NO:1 or SEQ ID NO:3" at paragraph [0009], for example.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D
Examiner
Art Unit 1642